Paper No. 32

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte YASUSHI SAITO,
MASAKI KITAHARA, MITSUAKI SAKASHITA,
KYOMI TOYODA, and TOSHIE SHIBAZAKI

Appeal No. 94-4009[1]
Application No. 07/953,716[2]

HEARD: 9 June 1999

Before WINTERS, GRON, and TORCZON, Administrative Patent Judges.

TORCZON, Administrative Patent Judge.

DECISION ON APPEAL

Appellants seek review under 35 U.S.C. § 134 from the final rejection of claims 5-7 and 11-24, all of the pending claims. We affirm.

BACKGROUND

Nissan Chemical Industries, Ltd. (Nissan) and Kowa Company, Ltd. are the assignees of record for the application on appeal (Reel 6328, frame 0835). Nissan is also the

[1] Attorney docket no. 49-177-OX.

[2] Application filed 30 September 1992.

assignee of record for the following three related patents for pharmaceutical compositions known as mevalonolactones:

Fujikawa et al., 5,011,930, issued 30 Apr. 1991 ('930);

Fujikawa et al., 5,024,999, issued 18 June 1991 ('999);

and

Fujikawa et al., 5,026,698, issued 25 June 1991 ('698).

Appellants state, and the prior art teaches, that "the compounds of Fujikawa et al[.]...are useful as curing agents against hyperlipidemia, hyperlipoproteinemia and atherosclerosis" (Paper No. 18 (App. Br.) at 7 (emphasis in original, citations omitted); '930 at 12:8-11; '999 at 26:31-34; '698 at 28:11-14).

The subject matter claimed in the present application is best illustrated in the sole independent claim, claim 11, which begins (Paper No. 8 (22 June 1993 Admt.) at 1-2):

> A method for inhibiting proliferation of aortic intimal smooth muscle cells, inhibiting migration of aortic medial smooth muscle cells into intima, or inhibiting adhesion of blood cells to endothelium, comprising administering to a patient in need thereof prior to atherosclerotic intimal thickening an effective amount of a compound of the formula (I):
>
> [Formula omitted].

Claims 22, 23, and 24, which depend from claim 11 via claims 19, 20, and 21,[3] respectively, identify compounds for use in the method as follows:

> 22. The method of claim 19, wherein said compound is (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-cyclopropyl-quinolin-3'-yl]hept-6-enoic acid, a compound having such carboxylic acid condensed with hydroxy at the 5-position to form a lactone, a sodium or calcium salt of such carboxylic acid, or a C_{1-3} alkyl ester of such carboxylic acid.
>
> 23. The method of claim 20, wherein said compound is (E)-3,5-dihydroxy-7-[6'-cyclopropyl-4'-(4"-fluorophenyl)-1',3'-dimethylpyrazolo[3,4-b]pyridin-5'-yl]hept-6-enoic acid, a compound having such carboxylic acid condensed with hydroxy at the 5-position to form a lactone, a sodium or calcium salt of such carboxylic acid, or a C_{1-3} alkyl ester of such carboxylic acid.
>
> 24. The method of claim 21, wherein said compound is (E)-3,5-dihydroxy-7-[6'-cyclopropyl-3'-ethyl-4'-(4"-fluorophenyl)-2'-methylthieno[2,3-b]pyridin-5'-yl]hept-6-enoic acid, a compound having such carboxylic acid condensed with hydroxy at the 5-position to form lactone, a sodium or calcium salt of such carboxylic acid, or a C_{1-3} alkyl ester of such carboxylic acid.

At the hearing, Appellants' counsel conceded that compounds of formula (I) are not new. This concession is consistent with our understanding that the genus of compounds in the claimed method includes compounds taught in the Fujikawa patents. Specifically, compound I-517 (Table I) of

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[3] These claims further limit claim 11 only by further defining the compound, not by adding additional steps.

the '930 patent is within the subgenus of claim 22; compound I-1-5 (Table 9) of the '999 patent is within the subgenus of claim 23; and compound I-1-7 (Table 7) of the '698 patent is within the subgenus of claim 24.

The examiner rejected all pending claims under 35 U.S.C. § 103 as having been obvious in view of each of the three Fujikawa patents in combination with Avery's Drug Treatment 594-595 (3d ed., Trevor M. Speight ed. 1987) ("Speight").

Appellants submitted as evidence in the record a declaration from co-inventor Masaki Kitahara (Paper No. 16) and an excerpt from W.C. Bowman & M.J. Rand, Textbook of Pharmacology, Second Edition, pp. 23.61-23.62 (1980) ("Bowman").

The claims directed to specific dose ranges and methods of administration (claims 15-17) were not separately argued (Paper No. 18 at 3). Nevertheless, we find that the claimed methods of administration and dosages are disclosed in the Fujikawa patents ('930 at 12:31-33 and 52-54; '999 at 26:54-56 and 27:7-9; '698 at 28:35-37 and 56-57).

DISCUSSION

To determine patentability under 35 U.S.C. §§ 102 and 103, one must first construe the claims. Key Pharm. Inc. v. Hercon Labs., 161 F.3d 709, 713, 48 USPQ2d 1911, 1915 (Fed.

Cir. 1998). We begin by construing the claims "to define the scope and meaning of each contested limitation." Gechter v. Davidson, 116 F.3d 1454, 1457, 43 USPQ2d 1030, 1032 (Fed. Cir. 1997). Claim 11 has three elements in addition to the compound: three purposes for the method, the subject of the method (a patient in need of the compound), and the time to treat the patient (prior to atherosclerotic intimal thickening). As noted previously, it is not contested that the Fujikawa patents teach administering the same compounds at the same effective dose. We may presume that identical compounds (here in the same effective dose) will have the same characteristics absent evidence to the contrary. In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

Purposes of the method

Claim 11 recites three purposes in the alternative:

- inhibiting proliferation of aortic intimal smooth muscle cells,
- inhibiting migration of aortic medial smooth muscle cells into intima, or
- inhibiting adhesion of blood cells to endothelium.

In each case the purpose is to inhibit rather than prevent the specified condition. The specification indicates

that the compounds may be used to inhibit after intimal thickening or even lesions have occurred:

> Accordingly, as a more effective inhibitor on atherosclerotic intimal thickening, a drug capable of directly acting on such atherosclerotic lesion, is desired. [Paper No. 1 (Spec.) at 2 (emphasis added).]

> The compound of the present invention may be [a] potent inhibitor [of] adhesion of blood cells (such as monocytes, macrophages), to endothelial cells, and may [] suppress the response of [the] early phase for atherosclerotic thickening. [Paper No. 1 (Spec.) at 6 (emphasis added).]

Since Appellants use the same compounds in the same dosages as Fujikawa, patients treated according to Fujikawa's teachings would be expected to obtain the same benefits. Thus, these purposes do not--by themselves--distinguish the claimed subject matter from Fujikawa's methods. In re Spada, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990) (A new use will not make an old compound patentable). The question remains, however, whether having one of these purposes further limits the steps of the method.

Administering to a patient in need thereof

The question this phrase of claim 11 presents is what is it that the patient is in need of? Grammatically, the "thereof" refers to an effective amount of the compounds to be administered. Cf. In re Hyatt, 708 F.2d 712, 714, 218 USPQ

195, 197 (Fed. Cir. 1983) ("A claim must be read in accordance with the precepts of English grammar."). As previously noted, an effective dose of Fujikawa's compounds is administered to patients affected with hypercholesterolemia, hyperlipidemia, and atherosclerosis. Thus far in the claim analysis, Appellants' patient population is the same as, or substantially overlapping with, Fujikawa's patient population: patients at-risk for or suffering hyperlipidemia or atherosclerosis.

Prior to atherosclerotic intimal thickening

To determine the proper meaning of claims, we first consider the intrinsic evidence (the claims, the written description and drawings, and the prosecution history).[4] Digital Biometrics, Inc. v. Identix, Inc., 149 F.3d 1335, 1347, 47 USPQ2d 1418, 1424 (Fed. Cir. 1998). The ordinary meaning of the words "prior to atherosclerotic intimal thickening" seems clear enough: the treatment must precede at least some intimal thickening. The claim language itself does not resolve whether treatment must occur before any intimal thickening. In this regard, the specification is helpful in

[4] However, even with intrinsic evidence, there is a hierarchy: the actual words of the claim are the controlling focus. Ordinarily, resort to extrinsic evidence should not be necessary. Id.

clearing up the ambiguity. As noted above, the purposes of the claim are met by inhibiting further atherosclerotic intimal thickening (Paper No. 1 (Spec.) at 2 and 6, supra). The specification reports suppression, not prevention, of the early phase of atherosclerotic intimal thickening (at 6). It also describes the compounds as acting directly on the atherosclerotic lesion (at 2), which appears to occur after intimal thickening has begun (cf. Bowman at 23.61, col. 2).

During prosecution, we are obliged to construe claims as broadly as is reasonable in view of the specification. In re Zletz, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989). At the hearing, counsel was invited to point to a definition in the specification of "prior to atherosclerotic intimal thickening". He indicated that the phrase is defined on page one of the specification. Although page one of the specification does not define "prior to atherosclerotic intimal thickening" with reasonable clarity, deliberateness, and precision, cf. In re Paulsen, 30 F.3d 1475, 1480, 31 USPQ2d 1671, 1674 (Fed. Cir. 1994), it does offer the following explanation of the initiation and progression of intimal thickening (Paper No. 1 (Spec.) at 1-2 (emphasis added)):

> As the onset mechanism, the atherosclerotic intimal thickening of coronary artery is believed to be one of the main causes for myocardial infarction and angina pectoris. This atherosclerotic intimal thickening is considered to be initiated by adhesion of monocytes or platelets to endothelial cells with secretion of cytokines and lipid accumulation and to be progressed by migration of [aortic medial smooth muscle cells] from the media to the intima and proliferation of the smooth muscle cells in the intima and increase of extracellular matrix, due to pathological and proliferative activation or modulation of smooth muscle cells. These activation[s] of the cells are promoted by risk factors such as hyperlipidemia. Heretofore, it has been reported that [3-hydroxy-3-methylglutaryl-coenzyme A] reductase inhibitors suppress the atherosclerotic intimal thickening by a strong effect to reduce serum cholesterol in an animal model..., but the effect in a clinical trial has been found inadequate.

Nothing in the preceding quote requires treatment before the initiation of intimal thickening. The quoted paragraph does, however, identify hyperlipidemia as a risk factor associated with activating smooth muscle cell proliferation and migration (second underlined sentence). The paragraph also associates the proliferation of aortic smooth muscle cells and their migration into the intima with atherosclerotic intimal thickening (first underlined sentence). We understand the specification to teach that hyperlipidemia, among other risk factors, may precede smooth muscle cell proliferation and migration, and thus precedes atherosclerotic intimal thickening.

Appellants argue that Bowman teaches conventional administration of Fujikawa's compounds would not occur until after atherosclerotic thickening occurs (Paper No. 18 at 9). Under the broadest interpretation of claim 11, this argument is not relevant since Fujikawa's compounds can be used to inhibit the further progression of the disease. Appellants' reference, Bowman, suggests that intimal thickening is part of the aging process, in which case treatment before any intimal thickening would be difficult (Bowman at 23.61, col. 2):

> In childhood, the intima of the arteries that are susceptible to atherosclerosis in later life consists predominantly of loose elastin fibres within a homogeneous matrix between the luminal endothelium and the internal elastic lamina (see [figure not of record]). With increasing age, smooth muscle cells from the media enter the intima through fenestrations in the elastic lamina and, and the extra cellular components of the connective tissue

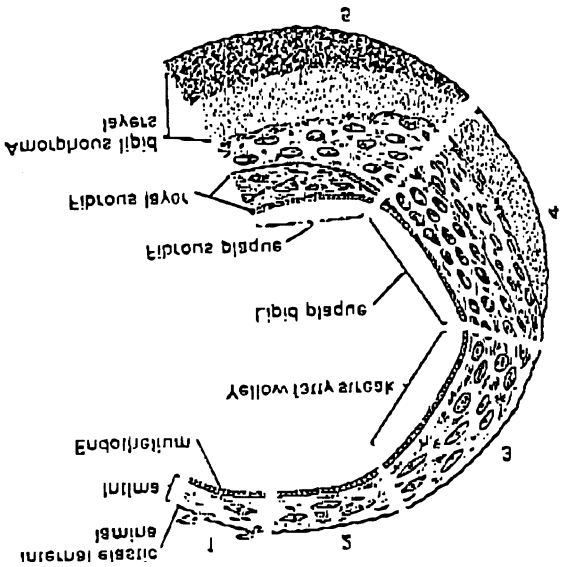

Fig. 23.24. Diagrammatic cross-section through intimal layer of artery wall to show stages of the development of theromatous plaques. 1. Normal intima; smooth muscle cells entering from media with increasing age. 2. Histological lesion; smooth muscle cells proliferating; increased deposition of fibres and perifibrous lipid. 3. Yellow fatty streak visible from intimal surface; smooth muscle cells transformed to foam cells containing intracellular lipid deposits. 4. Lipid plaque with three layers; lipid-filled cells; degenerating cells; amorphous lipid layer. 5. Fibrous plaque with four layers; fibrous layer; cellular layer with intracellular and extracellular lipid; inner amorphous lipid layer; outer amorphous lipid layer.

increase in thickness. At this stage, the lipid composition of the intima consists mainly of phospholipids (lecithins, cephalins and sphingomyelins; [cited pages not of record]). Some cholesterol is present, but cholesterol esters are generally absent.

We find nothing in Bowman that shows that atherosclerotic intimal thickening necessarily precedes other contributors to atherosclerosis like hyperlipidemia or hypercholesterolemia. We do, however, find a reasonable suggestion that it was conventional to delay both the development and the progression of atherosclerosis by treating hypercholesterolemia and hyperlipidemia (Bowman at 23.62, col. 2 ("Treatment of atherosclerosis")).

Even if we accepted Appellants' narrower construction that treatment must occur before any atherosclerotic intimal thickening had occurred, Appellants identify hyperlipidemia as a promoter of smooth muscle cell activation (Paper No. 1 (Spec.) at 2). Consequently, Fujikawa's hyperlipidemia patients would inherently be treated for atherosclerotic intimal thickening. Note that, since the claimed treatment begins prior to atherosclerotic intimal thickening, the patients are still healthy in terms of intimal thickening. Consequently, the clinician would have to have had some reason to suspect that the patient would benefit from prophylactic treatment for intimal thickening. At the hearing, we asked

counsel what symptoms would indicate that treatment in accordance with the method of claim 11 would be appropriate. He suggested a family history of atherosclerosis would suggest prophylactic treatment. The specification also suggests that hyperlipidemia is an indication. Fujikawa's compounds are useful for treating hyperlipidemia. Early treatment of hyperlipidemia patients would at least often (and prophylactic treatment of otherwise asymptomatic patients would necessarily) occur before atherosclerotic intimal thickening. See In re Woodruff, 919 F.2d 1575, 1578, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990) ("It is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable.").

After reviewing the evidence of record, we find that the method described in each Fujikawa patent anticipates claim 11. This finding is not a new ground of rejection because anticipation is the epitome of obviousness, so the subject matter of anticipated claims is necessarily obvious. Paulsen, 30 F.3d at 1481, 31 USPQ2d at 1675; In re Baxter Travenol Labs., 952 F.2d 388, 391, 21 USPQ2d 1281, 1285 (Fed. Cir. 1991)).

Claims 12-14 are directed to therapeutic benefits that we found to be inherent in the early use of Fujikawa's compounds.

Claims 22-24 recite specific compounds that we found to be specifically identified in the Fujikawa patents.

Unexpected results are not germane to an anticipatory disclosure since the claimed subject matter is old in the art. Kitahara's declaration cannot make an old invention new. We note, however, that Kitahara's declaration is not effective for its intended purpose. "[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared to with the closest prior art." Baxter Travenol, 952 F.2d at 392, 21 USPQ2d at 1285. Kitahara provides results comparing Pravastatin and Clinofibrate, both apparently unrelated compounds (see the figures in Paper No. 1 (Spec.) at 51 and Paper No. 16 at 2), with Test Compound 1 (see Paper No. 1 (Spec.) at 51). The closest related compound in the prior art is the last I-2 compound in Table 1 of the '930 Fujikawa patent (11:65), where the carboxyl group has condensed with the 5-hydroxy to form a lactone (see Fujikawa '930, 12:14-17, teaching administration in the lactone form). The evidence of record indicates that a comparison with the closest prior art compound, Fujikawa '930 I-2, which is identical to Test Compound 1, would have revealed no difference at all. Just as unexpected beneficial results support unobviousness, expected beneficial results suggest

obviousness. In re Skoll, 523 F.2d 1392, 1397, 187 USPQ 481, 484 (CCPA 1975). Recognition of an inherent property is not a basis for rebutting a prima facie finding of obviousness. Baxter Travenol Labs., 952 F.2d at 392, 21 USPQ2d at 1285.

Alternatively, the preponderance of the evidence of record supports a conclusion of obviousness for claim 11. Speight provides motivation for early preventative treatment of at-risk patients with appropriate drug treatment (p. 594, § 3.1.3). High plasma lipid levels are a risk factor (id.). Fujikawa's compounds are conceded to be useful in treating hyperlipidemia (Paper No. 18 at 7). Thus, a person having ordinary skill in the art would have been motivated to treat at-risk patients for hyperlipidemia early to prevent the development of atherosclerosis. Treating patients early for hyperlipidemia inherently inhibits intimal thickening.

DECISION

We affirm the rejection of claims 5-7 and 11-24, all of the pending claims. The period for taking any subsequent

action in connection with this appeal will be extended only under the limited circumstances provided in 37 CFR § 1.136(b).

AFFIRMED

SHERMAN D. WINTERS
Administrative Patent Judge

TEDDY S. GRON
Administrative Patent Judge

RICHARD TORCZON
Administrative Patent Judge

BOARD OF PATENT APPEALS AND INTERFERENCES

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